No. 17-1480

IN THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

SANOFI; SANOFI-AVENTIS U.S. LLC;
AVENTISUB LLC, F/D/B/A AVENTIS PHARMACEUTICALS INC.; AND
REGENERON PHARMACEUTICALS, INC.,

Defendants-Appellants

v.

AMGEN INC.; AMGEN MANUFACTURING, LIMITED;
AND AMGEN USA, INC.,

Plaintiffs-Appellees

On Appeal from the United States District Court
for the District of Delaware
No. 14-CV-1317-SLR

AMGEN'S OPPOSITION TO PROPOSED AMICI PROVIDERS' AND PATIENTS' MOTION FOR LEAVE TO FILE AMICUS CURIAE BRIEF

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March 6, 2017

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CERTIFICATE OF INTEREST

Counsel for Plaintiffs-Appellees Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc. certifies the following:

1. The full names of the parties represented by me are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

2. The names of the real parties in interest are Amgen Inc.; Amgen Manufacturing, Limited; and Amgen USA, Inc.

3. Amgen Inc. owns 10 percent or more of the stock of Amgen Manufacturing, Limited and Amgen USA, Inc. No publicly held company owns 10 percent or more of Amgen Inc.

4. The names of all firms and the partners or associates that appeared for the parties now represented by me in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

AMGEN INC.: Stuart L. Watt; Wendy A. Whiteford; Erica S. Olson; Dennis J. Smith; Emily C. Johnson; Steven Tang

YOUNG CONAWAY STARGATT & TAYLOR: Melanie K. Sharp; James L. Higgins

McDERMOTT WILL & EMERY LLP: William G. Gaede, III; Sarah C. Columbia; Michael V. O'Shaughnessy; Mandy H. Kim; K. Nicole Clouse; Lauren Martin; Eric W. Hagen; Rebecca Harker Duttry; Bhanu K. Sadasivan

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KING & SPALDING LLP: Daryl L. Joseffer; Merritt E. McAlister; Christopher R. Healy; Joshua N. Mitchell; Hon. Adam M. Conrad (no longer with the firm)

March 6, 2017 /s/ Daryl L. Joseffer

Daryl L. Joseffer

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Rather than provide appropriate perspective on the issues raised by Appellants on appeal, the proposed amicus brief attempts to supplement the record with unsubstantiated factual assertions contradicted by the trial record. Appellants offered this evidence in the district court, but Amgen showed these points to be unfounded in fact and the district court did not credit them.

The privilege of being heard as amicus depends on whether the proffered information is desirable, relevant, timely, and useful. *See* Fed. R. App. P. 29(a)(2), (a)(3)(B); 3A C.J.S. Amicus Curiae § 3. The proposed amicus brief attempts to confuse the factual record, is unhelpful, and takes positions that are misleading and fearmongering.[1]

I. The Proposed Amicus Brief Would Improperly Supplement the Record

The question before the Court is whether the district court abused its discretion in enjoining Appellants' infringing product following a stipulation of infringement, a jury verdict of validity, a two-day hearing on whether to grant injunctive relief, and full briefing on that question.

[1] Some of the same medical providers attempted to introduce similar evidence when the Court considered whether to stay the district court's injunction pending appeal. DE33, DE36. Amgen opposed that request for similar reasons, DE49-1, and this Court denied the motion for leave as moot when it granted the stay. DE59.

Unsubstantiated evidence that was not before the district court has no value to this Court in answering that question. The proposed brief is just that. The Proposed Amici—several providers who prescribe Appellants' infringing biologic, Praluent, and two patients who take Praluent—attempt to supplement the record with what amounts to untested, unsworn, and speculative testimony.

An amicus brief that attempts to expand a closed factual record is improper. *See* Allison Orr Larsen, *The Trouble With Amicus Facts*, 100 Va. L. Rev. 1757, 1772, 1784 (2014) ("These briefs are filed after the record is closed, and the information they present is not subject to cross-examination below"; instead, "the factual data" presented by amici "are all funneled through an advocacy sieve."). It is well-settled that "the record on appeal is generally limited to that which was before the trial court," and "any authority to enlarge the record 'is rarely exercised and is a narrow exception' to the general rule limiting the record to that considered below." *CW Gov't Travel, Inc. v. United States*, 163 F. App'x 853, 860 (Fed. Cir. 2005) (non-precedential). Because the evidence is "not in the record on appeal," this Court should not consider it in assessing the propriety of the injunction. *SkinMedica, Inc. v. Histogen Inc.*, 727 F.3d 1187, 1208 (Fed. Cir. 2013).

Had Appellants presented these witnesses in the district court a year ago, Amgen would have shown their assertions to be false through discovery and cross-examination—the "greatest legal engine ever invented for the discovery of truth," *Lilly v. Virginia*, 527 U.S. 116, 124 (1999). And Amgen's expert witnesses could have responded to their testimony.

The inability to test witnesses through discovery and cross-examination—including for objectivity—is particularly problematic here. For example, the proposed brief does not disclose that a federal jury unanimously found that Proposed Amicus Dr. Mary McGowan had defamed, with malice, Dr. Evan Stein. *Stein v. McGowan*, No. 1:12-cv-00695-SKB, ECF No. 77, at 5–6, 9–10 (S.D. Ohio Feb. 25, 2015), *appeal dismissed per stipulation of the parties*, No. 15-3327, ECF No. 23 (6th Cir. May 28, 2015). Dr. Stein is Amgen's medical expert who testified on the same topics now addressed in the proposed brief. Nor does the brief disclose that some of the Proposed Amici have received payments and funding from Appellants. *See, e.g.*, Open Payments Data for Luis

Aparicio, M.D. reported by Centers for Medicare & Medicaid Services, *available at* http://bit.ly/2lx17e8 (reporting 79 payments totaling $35,426.88 from 2013 to 2015 paid by Sanofi-Aventis U.S. LLC to Dr. Aparicio).

II. The Proposed Amicus Brief Offers Conclusory Speculation Contradicted By The Trial Record That Would Be Unhelpful to the Court

The proposed brief offers conclusory, untested, unsworn, and speculative testimony of the Proposed Amici and can be of no use to the Court. The proposed brief is rife with assertions that *do not even cite a source*—whether in the record or not. More importantly, these assertions are contradicted by the existing record.

A. Proposed Amici Provide No Support For Second-Guessing The FDA's Determination That Repatha Can Meet The Needs Of All Affected Patients.

Proposed Amici contend that an injunction will expose patients currently taking Praluent to health risks by depriving them of useful medicine. Proposed Br. at 18–20. There is no doubt that the antibody products described and claimed in Amgen's patents, and embodied by Amgen's Repatha and the infringing Praluent, are a significant breakthrough compared to prior treatments to lower cholesterol, such as the use of drugs known as "statins." But that has no bearing here because Amgen's Repatha can meet the needs of all patients.

The FDA approved Repatha to safely and effectively treat all patients covered by the Praluent label. *See* Ex. A (Perm. Inj. Order, Dist. Ct. ECF No. 392) at 6; Ex. B (Inj. Hr'g Tr.) at 86:14–87:5 (Stein testimony); Ex. C. (JTX-392, Repatha label); Ex. D (PTX-5012, Praluent label). The district court considered all of the evidence and declined to second-guess the FDA on this point. Ex. A at 6.

Proposed Amici baldly assert that some patients have failed to respond to Repatha but responded to Praluent. Proposed Br. at 18. But they provide nothing besides their own say-so in support. Surely, if evidence existed that patients respond to Praluent but not Repatha, Appellants would have cited and indeed emphasized it to the district court. They did not because there is no such evidence.

B. Proposed Amici Offer Duplicative and Speculative Opinions Regarding Safety of "Very Low" LDL Cholesterol Levels

Proposed Amici echo Appellants' assertion that enjoining Praluent, which offers a *starting* dose of 75 mg, will put patients at risk because of a speculative fear of patients' LDL cholesterol levels going "too low." This argument was fully litigated below and rejected by the district court, which declined to second-guess the FDA. Ex. A at 6. The FDA labeling on *both* Repatha and Praluent states that there is "no evidence" of a safety risk from very low LDL-C levels. Ex. C at '372–73; Ex. D at '249; *see also* Ex. B at 105:18–106:12 (Stein testimony).

Despite thorough investigation over many years, the record contains no evidence of any safety risk from "very low" LDL cholesterol levels. *See* Ex. B at 97:7–101:18 (Stein testimony); 436:10–19 (Eckel testimony); Ex. E (PTX-4976, Praluent FDA briefing document) at '663 and '704–07; Ex. F (PTX-4983, Repatha FDA briefing document) at '932. To the contrary, patients with "very low" LDL cholesterol levels reported a *lower* occurrence of adverse events in Appellants' own clinical trials. Ex. B at 99:22–100:16, 106:13–15, 108:19–109:17 (Stein testimony); Ex. E at '663, -704–07; Ex. G (PTX-4973, Praluent EMDAC presentation) at '907–08, '982. More than 900 patients in the Praluent clinical trials had measured LDL-C levels below 25 mg/dL without experiencing any increased risk of adverse events. Ex. B 99:7–101:19; 436:10–19; 279:15–20; Ex. G at '981–82; *see also* Ex. E at '663, '704–07; Ex. C; Ex. D.

The proposed brief cites two extra-record articles to support Proposed Amici's speculation. One article is a non-peer-reviewed internet piece that consists of a mere twelve sentences and does not even address PCSK9 inhibitors. Proposed Br. at 19 (citing Lopez-Jimenez, *Cholesterol level: Can it be too low?*, MAYO CLINIC (Oct. 30, 2015)). This internet piece does not and could not identify a causal link between any health risk and very low LDL-C levels. Lopez-Jimenez, *supra*.

The other article was funded by Appellants and co-authored by their stockholders and employees during this litigation. Proposed Br. at 19–20 (citing Robinson et al., *Safety of Very Low Low-Density Lipoprotein Cholesterol Levels With Alirocumab*, 69 J. AM. COLLEGE OF CARDIOLOGY 471 (2017)); *see* Robinson et al., *supra*, at 471–72 (disclosures following notes a–h). This article analyzed the same Praluent clinical data that was addressed before the district court and found that the patients that achieved LDL-C levels below 25 mg/dL generally had similar rates of adverse events compared to both the control group and patients with LDL-C levels at or above 25 mg/dL. Robinson et al., *supra*, at 476, 478 at Table 2.[2]

If the Court wishes to consider extra-record evidence, additional data generated since the injunction hearing continue to confirm the safety and benefits of "very low" LDL cholesterol levels. The results of the GLAGOV study, published in the *Journal of the American Medical Association* in November 2016, showed that 80% of patients achieving "very low" levels of LDL-C on Repatha had a reduction in plaque build-up in their arteries with no attendant safety concerns. *See* DE56-41 (Ex. NN to Amgen's Opp. to Stay Pending Appeal, Stein declaration) ¶ 35 & DE56-28 (Ex. AA, Nicholls et al., *Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial*, 316 J. AM. MED. ASS'N 2373, 2380–81 (2016)).[3]

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[2] Proposed Amici cite the article for the proposition, not advanced by Appellants, that "too low LDL-C levels can increase the risk of cataracts." Proposed Br. at 19. But that conclusion came from the use of Appellants' Praluent not Amgen's Repatha.

[3] Amgen does not believe extra-record evidence would be helpful to Court in assessing the injunction issues before it, but cites to the stay briefing before this Court solely for the purpose of demonstrating the one-sided and untested view of the unsupported statements put forward by proposed amici.

C. Proposed Amici Erroneously Claim That Repatha Does Not Have a Latex-Free Option

The proposed brief incorrectly states that "Praluent is latex-free while Repatha is not." Proposed Br. at 20. It claims that a patient allergic to latex cannot take Repatha and suggests for that reason that Praluent should not be enjoined. But Repatha does not contain latex. Although one method of administering Repatha entails the use of needle covers containing dry natural rubber, another method (the latex-free Pushtronex device) does not contain any latex. *See* Amgen's Opp. to Stay Pending Appeal, DE56-42 ¶ 15 (Broadhurst declaration) ("[T]he FDA recently approved Amgen's Pushtronex™ device . . . ."); Repatha label, Rev. 7/2016, p. 16 (Patient Information), *available at* http://bit.ly/2mxkmEb ("The single-use Pushtronex™ system . . . is not made with natural rubber latex."). When a Regeneron witness raised the specter of latex allergies in the district court, he later conceded that "there were no adverse events in the clinical trials for Repatha with respect to latex." Ex. B at 307:6–11; 310:17–22. The amicus brief would pile unsupported speculation on unsupported speculation.

D. Proposed Amici Have No Basis for Offering Speculative Opinions on Insurance Negotiations and Pricing

Proposed Amici suggest that if Praluent were removed from market, insurers who currently exclusively cover Praluent would not be in a position to cover Repatha, thereby leaving patients without needed care. They state that they "understand" that renegotiating contracts with those insurers who cover Praluent but not Repatha could take "six months or longer." Proposed Br. at 21. Where this understanding comes from they do not say—but it certainly did not come from the evidence in this case. Testimony at the injunction hearing established that insurance contracts can be negotiated "within 24 to 48 hours," and that "[r]arely" will it take longer than "two or three weeks," when there is one product available for a novel therapeutic class. Ex. B at 142:14–21. At the injunction hearing, Amgen established its ability to supply and support the entire PCSK9 antibody market, and Amgen is well positioned to assist patients transitioning from Praluent to Repatha quickly and easily. Ex. B at 515:10–22 (Broadhurst testimony); *see also* Amgen's Opp. to Stay Pending Appeal, DE56-1 at 30–31; DE56-41

¶¶ 19–20 (Stein declaration); DE56-42 ¶¶ 17–19, 21–29 (Broadhurst declaration); DE56-43 ¶ 18–21 (Berndt declaration).

Likewise, Proposed Amici's concern about potential price increases offers nothing helpful. This Court has consistently rejected the argument that any price reduction that might result from competition outweighs "the significant 'public interest in encouraging investment in drug development and protecting the exclusionary rights conveyed in valid pharmaceutical patents.'" *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1362–63 (Fed. Cir. 2008) (quoting *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1383 (Fed. Cir. 2006)); *see also* Ex. B at 239:8–240:11 (Berndt testimony). Moreover, Proposed Amici provide no evidence that the injunction will lead to runaway price increases for patients. As the district court record shows, insurers use competition to negotiate deeper price discounts for *themselves* (*i.e.*, discounts off the wholesale acquisition cost), but these discounts are not realized by patients as a discount in their prescription costs. Ex. B at 141:6–13 (Ryan testimony); *id.* at 164:15–24 (Broadhurst testimony); *see also* DE56-42 ¶ 14 (Broadhurst declaration); DE56-43 ¶ 24 (Berndt declaration).

E. Proposed Amici's Speculation Regarding Harm to Future Clinical Research Is Without Basis

Finally, Proposed Amici's conclusory speculation that the injunction would interfere with clinical trials is unfounded. Proposed Br. at 23–24. The Patent Act provides a safe harbor from infringement for the use of a patented invention in clinical trials "reasonably related to the development and submission of information" to the FDA. 35 U.S.C. § 271(e)(1); *Merck KgaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005). Amgen has never taken the position that the injunction should prohibit clinical trials within the scope of Section 271(e)'s safe harbor.

The idea that clinical research on PCSK9 therapy will evaporate because of lack of patient interest if the injunction is affirmed is not credible. Proposed Br. at 23. First, most clinical trial patients enrolled before Praluent even had regulatory approval so there was no guarantee that it would be approved and marketed. DE56-41 ¶ 58 (Stein declaration). Second, no patients are guaranteed to receive Praluent during clinical trials; Appellants' clinical studies are double-blinded and randomized, such that half the patients receive placebo. *Id.* ¶ 57.

III. Vacating the Injunction Most Certainly Would Deny Amgen a Remedy

Proposed Amici's argument that monetary damages are adequate does nothing more than repeat conclusory arguments the district court rejected. As that court found, Amgen has demonstrated irreparable harm for which it cannot fully recover with monetary damages, including loss of market share and momentum, damage to its bargaining position vis-à-vis insurance contracts, and immeasurable reputational harm. Ex. A at 5, 7.

* * *

Proposed Amici offer no useful perspective that would justify vacating the permanent injunction. Instead, their brief provides a collection of conclusory, unsupported speculation and uncorroborated, untimely testimony. The Court should deny their motion for leave to file.

Dated: March 6, 2017

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CERTIFICATE OF COMPLIANCE

I certify that the foregoing complies with the type-volume limitation of Fed. R. App. P. 27(d) because it contains 2,462 words, excluding the parts exempted by Fed. R. App. P. 32(f).

I further certify that the foregoing complies with the typeface and type style requirements of Fed. R. App. P. 32(a) because it has been prepared in a proportionally spaced typeface using Microsoft Word in 14-point font.

March 6, 2017

/s/ Daryl L. Joseffer
Daryl L. Joseffer

CERTIFICATE OF SERVICE

I certify that on March 6, 2017, I caused the foregoing to be filed with the Court electronically using the CM/ECF system, which will send a notification to all counsel of record.

March 6, 2017

/s/ Daryl L. Joseffer
Daryl L. Joseffer